

INTRAMOLECULAR ANODIC CYCLISATION OF PHENOLS AND PHENOL ETHERS

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av

Ulf Palmqvist
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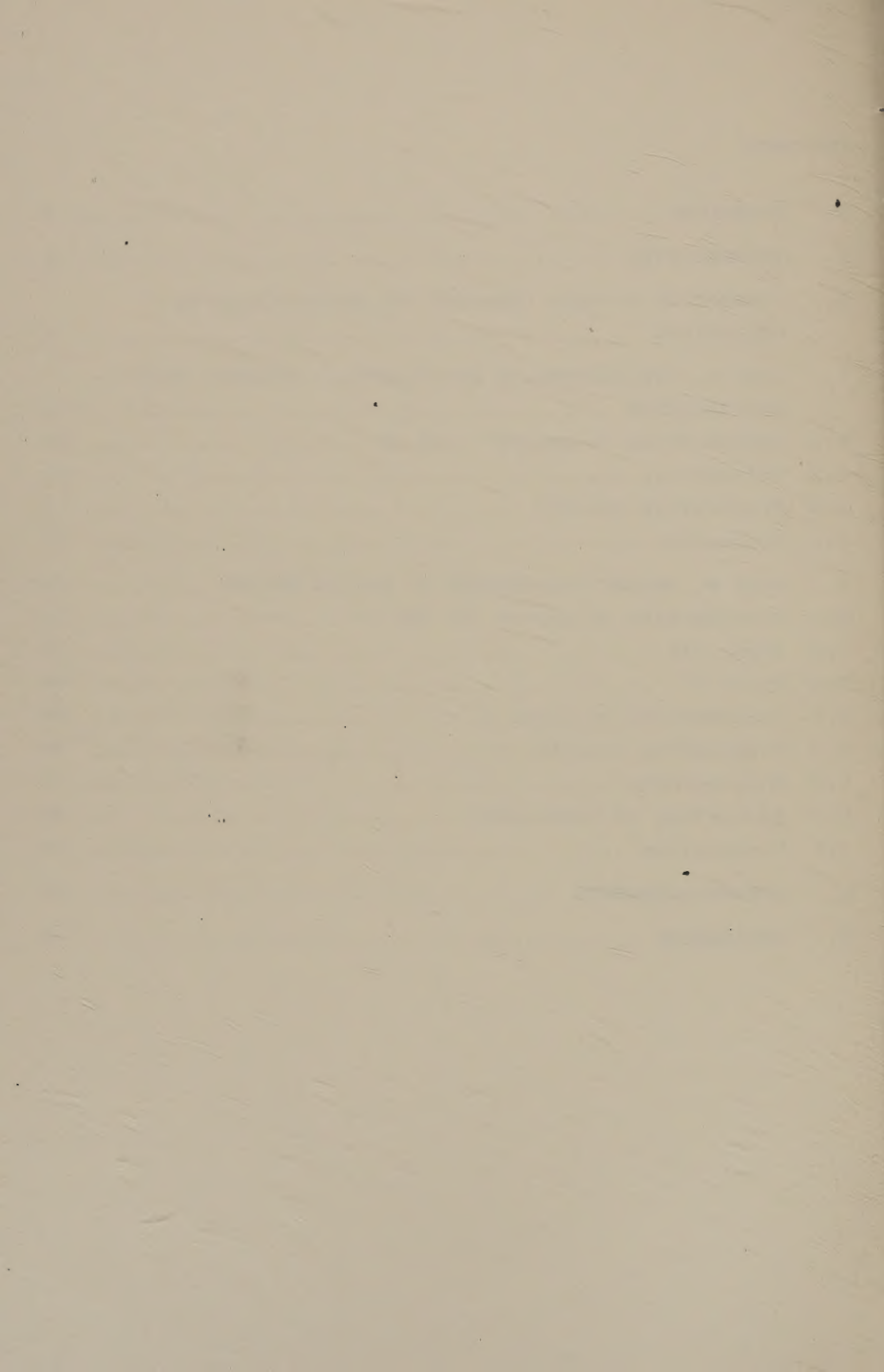
INTRAMOLECULAR ANODIC CYCLISATION
OF PHENOLS AND PHENOL ETHERS.

Ulf Palmqvist

Organic Chemistry 2, Chemical Center, The Lund Institute of
Technology, Box 740, S-220 07 Lund 7, Sweden.

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1. FOREWORD.

The work presented in this thesis deals with the intramolecular anodic cyclisation of phenols (part A) and phenol ethers (part B). The following papers are summarised. (Referred to in text by roman numerals I-V.)

- I U. Palmqvist, A. Ronlán and V. D. Parker. Intramolecular coupling of diarylpropanes. Evidence for phenoxoniumion mechanism. *Acta Chem. Scand.* 28, 267 (1974).
- II U. Palmqvist, A. Nilsson, V. D. Parker and A. Ronlán. Anodic oxidation of phenolic compounds 4. Scope and mechanism of the anodic intramolecular coupling of phenolic diarylalkanes. *J. Amer. Chem. Soc.* 98, 2571 (1976).
- III V. D. Parker, U. Palmqvist and A. Ronlán. The direct observation of intermediates during the oxidative cyclisation of phenol ethers. *Acta Chem. Scand.* 28, 1241 (1974).
- IV A. Nilsson, U. Palmqvist, A. Ronlán and V. D. Parker. Effect of forced coplanarity of biphenyl rings on the ease of formation and stability of phenolic cations. *J. Amer. Chem. Soc.* 97, 3540 (1975).
- V U. Palmqvist, A. Nilsson, V. D. Parker, T. Pettersson and A. Ronlán. Anodic oxidation of 1,2,3,4-tetrahydronaphthalene and isochromane analogues of 1-benzyl and 1-phenethylisoquinoline alkaloids. Products and mechanism of the intramolecular cyclisation. Submitted for publication.

The main purpose of this study has been to examine the anodic coupling of a variety of different substrates in order to

- a) elucidate the involved reaction mechanisms
- b) demonstrate the synthetic utility of anodic oxidations

The following modes of coupling were identified with reasonable certainty. (See also remarks of D. H. R. Barton in the foreword to Ref.1.)

- a) $\text{ArR}^{\cdot+} + \text{ArR} \rightarrow \text{ArR}^+ - \text{ArR}^{\cdot-} \xrightarrow{-e} \text{Ar}-\text{Ar} + 2\text{R}^+$
- b) $\text{ArR}^{\cdot+} + \text{ArR}^{\cdot+} \rightarrow \text{Ar}-\text{Ar} + 2\text{R}^+$
- c) $\text{Ar}^{\cdot} + \text{Ar}^{\cdot} \rightarrow \text{Ar} + \text{Ar}$
- d) $\text{ArR}^{\cdot+} + \text{Ar}^{\cdot} \rightarrow \text{Ar}-\text{Ar} + \text{R}^+$
- e) $\text{Ar}^+ + \text{ArR} \rightarrow \text{Ar}-\text{Ar} + \text{R}^+$

(ArR = phenol ($\text{R} = \text{H}$) or phenol ether ($\text{R} = \text{Alkyl}$.) In the case of phenols $\text{ArR}^{\cdot+}$ is very short-lived in neutral solutions and therefore only c) and e) are operative with these substrates.)

The anodic oxidations studied here frequently proceed by two or more of the paths simultaneously and clean reactions were seen only under special circumstances.

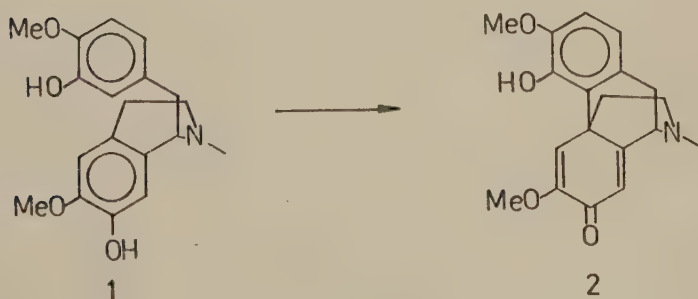
The synthetic possibilities of these anodic techniques appear to be comparable to other electron transfer reactions. However it is easier to elucidate the nature of the reactions during electrolysis (with diverse electroanalytical methods). The reaction conditions are therefore more readily optimised than for "chemical" electron transfer reagents.

During the seventies a few very good coupling reagents for phenols (i.e. $\text{Ti}(\text{CF}_3\text{CO}_2)_3$) have appeared which are comparable or better than anodic oxidation. However these reagents

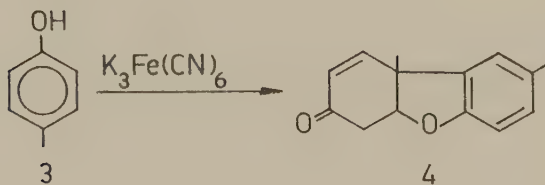
do not function by electron transfer and consequently they have limited applicability for the oxidation of phenol ethers. Electrochemical procedures should therefore find greater use in the future, particularly for coupling of phenol ethers.

2. INTRODUCTION

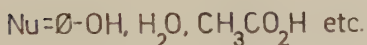
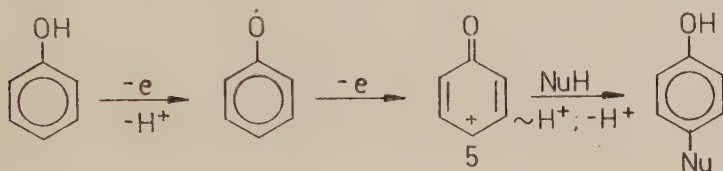
Oxidation of phenols or phenol ethers to effect coupling or substitution is a very common step in the biosynthesis of many natural products. Cyclisation of reticuline 1 to salutaridine 2 in the biogenesis of morphine is an example from the field of alkaloids.



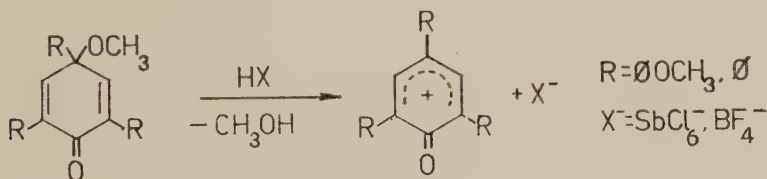
In accordance with the importance of the reaction there have appeared many papers dealing with the subject. (For reviews see 1 and 2.) The early experiments achieved only limited success as far as yield and an understanding of the underlying mechanisms were concerned. Many different reagents including $K_3Fe(CN)_6$, $FeCl_3$, $K_2S_2O_8/OH^-$, MnO_2 and $ON(SO_3K)_2$ have been tested. One early success however was the oxidation of p-cresol 3 to Pummerer's ketone, 4, with $K_3Fe(CN)_6$.



The mechanism for this reaction was believed to involve coupling of two initially formed phenoxyl radicals. For a long time the results were interpreted as a consequence of a radical coupling mechanism. In the middle of the fifties however there appeared suggestions^{5,6} that coupling or substitution of phenols might also occur by nucleophilic attack on a phenoxonium ion, 5.



Since then phenoxonium ions have been observed both directly and indirectly⁷.



These two mechanisms, radical coupling and nucleophilic attack on a phenoxonium ion, can account for almost all couplings and substitutions. However, in many cases there are other mechanisms which, theoretically at least, explain the results equally well.

3. COMPARISON BETWEEN CHEMICAL AND ELECTROCHEMICAL OXIDATIONS.

In order to clarify the picture and at the same time to give some of the background to our own investigations in the field it is worthwhile outlining somewhat more closely the sequence of events when phenols or phenol ethers couple after electron loss.

Fig. 1 shows, as an example, all the conceivable routes to spirocyclohexadienones from α , ω -diphenyletheralkanes (or α -phenylether ω -phenolalkanes when R=H). (Some of the intermediates are purely hypothetical and have been included only for the sake of completeness.)

Electrochemists often use the symbols E and C (see Fig. 1) to specify the events that take place in an electrochemical process. As can be seen the sequence from substrate to product always consists of two E- plus three C-reactions. The order in which the E:s and the C:s occur can vary. (This generalization holds for all electrochemical reactions which do not result in products carrying a different charge from that of the substrate.) Obviously the sequence of events must start with an electron transfer reaction and end with a bond making or bond breaking step. The possible mechanisms are then EECC, ECECC and ECCEC. This simplicity is not however quite real. As can be seen from Fig. 1 there are three possible intermediates after an EE-sequence and four possible intermediates after an EC-sequence and so on (EEC:5, ECE:3, ECC:2). Now one can always ask if there is a real difference between, for instance, a diradical dication and a dication both of which are EE-intermediates. It is possible to argue that electron transfer reactions within a molecule can be so fast that the two are best considered more or less as mesomeric forms of one intermediate. However as soon as a C-reaction (which is not a cyclisation) has been interposed in the se-

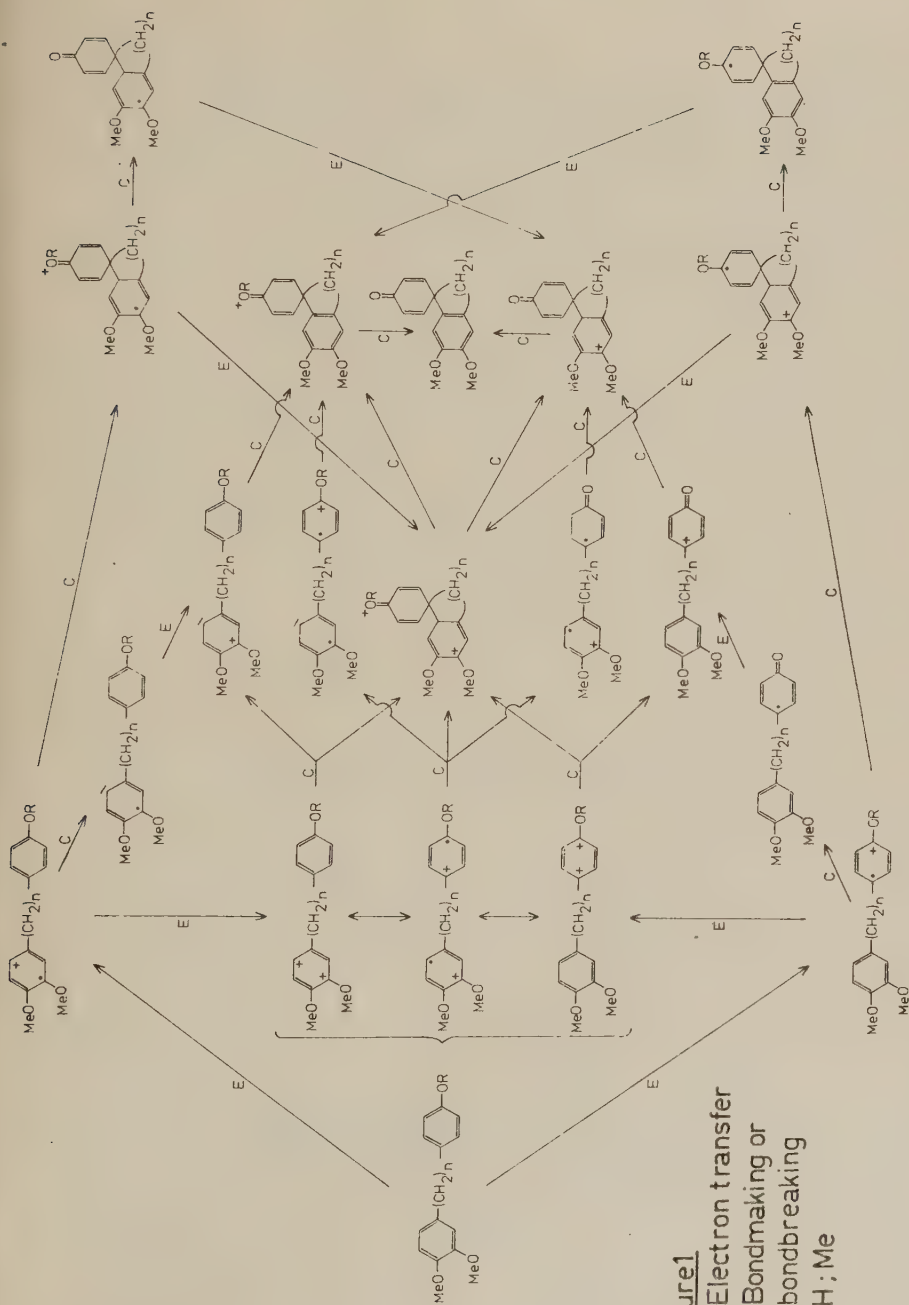


Figure1
E = Electron transfer
C = Bondmaking or
bondbreaking
R = H; Me

quence this argument does not hold since the two intermediates will have different molecular formulae. This means that all five EEC-intermediates in the example (Fig. 1) must be considered as discrete intermediates. (However they will have different probabilities, see discussion below.)

When starting experiments in the field of electron transfer reactions it is advisable to have a picture such as Fig. 1 in mind. Fig. 1 shows only intermediates leading to spirodienones. Since all intermediates can enter other sequences leading to other products (cyclisation to other positions, intermolecular coupling, reaction with nucleophiles in the solution etc.) it is easy to understand why electron transfer reactions often lead to a large number of products.

Oxidation reagents that do not function by electron transfer (e.g. $\text{Ti}(\text{OCOCF}_3)_3$, $\text{Pb}(\text{OAc})_4$, CrO_3 etc.) unlike electron transfer reagents almost always react to give a single well-defined intermediate. Fig. 2.

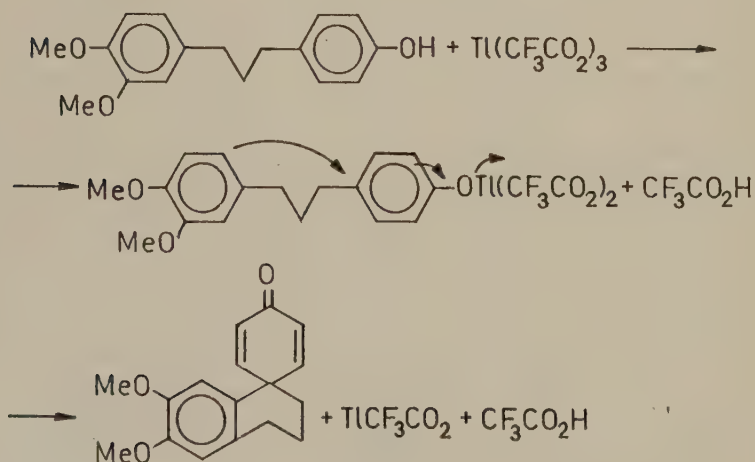


Figure 2

When a well-defined intermediate of this type is formed it is always easier to make generalizations. The ester (in the case shown in Fig. 2) functions as a "handle" and very largely determines the outcome of a reaction by its own electronic and steric requirements. In electron transfer reactions there are no such "handles" and the outcome is thus much more dependent on more subtle effects such as solvent-solute interactions. In this light it is easy to understand why electron transfer reactions are often difficult to predict. In spite of the apparent simplicity the parameters must very often be controlled more carefully in electrochemistry than in "classical" chemistry.

The radical cation is a good example of the situation. In principle this species can react in three ways, as a radical, as an electrophile and as an acid. It is very important to know if and how it is possible to force this species to react cleanly in only one of these ways.

So far the discussion has dealt with the loosely defined concept "electron transfer". However while there is no essential difference between "chemical" reagents and the electrode, from a more practical standpoint, notably the possibility of elucidating reaction mechanisms, there are great differences. During the last two or three decades there have been considerable advances in electro-analytical chemistry which make it possible to observe directly a number of very transient intermediates. Among these techniques are the polarographic methods cyclic voltammetry, ac-polarography and the use of rotating disc and rotating ring disc electrodes⁸.

The probabilities of formation of the intermediates shown in Fig. 1 were not dealt with above. There are of course large differences. Some of the more important will be discussed here in order to give a better comprehension of discussions below.

First it is safe to assume that radical cations from phenols in most solutions lose the hydroxyl proton and yield a radical in the first step⁹. This, combined with the fact that oxidation potentials for monohydric phenols and dimethoxy benzenes are comparable makes all three EE-intermediates from the substrate with R=H highly improbable. The upper two EE-intermediates are however quite conceivable in oxidation of the substrate with R=Me. The normal course of reaction for the upper E-product would be loss of Me⁺ rather than H⁺. (But then the desired product can not be formed.) The radical carbene shown in Fig. 1 must be regarded as highly improbable. The same certainly holds for the uppermost EEC (or ECE) intermediate, which is a cation-carbene!

4. PART A.

CYCLISATION OF SUBSTITUTED α -PHENOL- ω -PHENYLETHERALKANES

4:1 Introduction to papers I and II.

There are three main reasons why the model compounds chosen are well suited for a study of reactions such as those depicted in Fig. 1 which can proceed by a large number of different routes.

1) By arranging for intramolecular coupling instead of intermolecular coupling a much higher effective concentration of reactants can be achieved.

A comparison between intermolecularly and intramolecularly catalysed hydrolysis provides an example showing that this effect is real. (Ref. 10) Fig. 3.

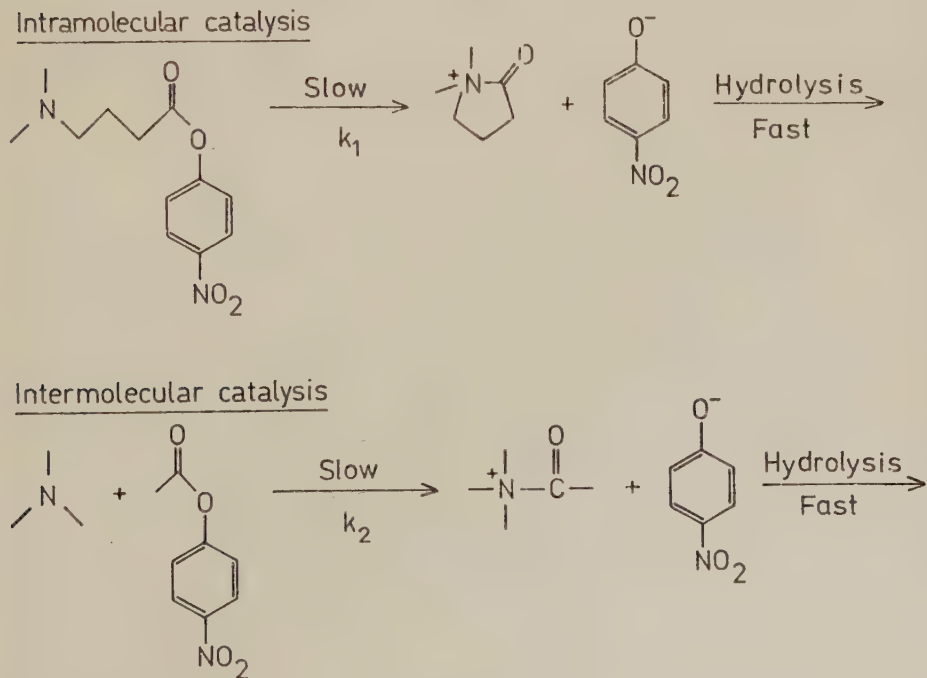


Figure 3

The parameters of activation are very similar and there is little doubt that the same mechanism is involved in both reactions. The quotient k_2/k_1 has the dimension $|\text{mol sec/sec}| = \text{mol}$ and can be regarded as the fictional concentration of trimethylamine which would be necessary to achieve comparable catalysis to that in the intramolecular case. This concentration is 5370 molar!

2) The spirocyclohexadienones always have higher oxidation potentials than the substrate and consequently it should be easy to avoid complications from further oxidation.

3) By proper substitution it is possible to oxidise the phenol part or the phenol ether part selectively, thereby enabling study of all the pathways depicted in Fig. 1.

The substances investigated and the spirodienones obtained together with (approximate) oxidation potentials for each ring and for the substance as a whole are shown in Fig. 4.

4:2 Voltammetry.

Some typical voltammograms in $\text{CH}_3\text{CN}/\text{LiClO}_4$ or $\text{CH}_2\text{Cl}_2/\text{TFMS}/(\text{nBu})_4\text{NBF}_4$ are shown in Fig. 5. The voltammograms for all the substances are very similar under both sets of conditions except in one case (8 in methylene chloride-trifluoromethanesulphonic acid ($\text{CH}_2\text{Cl}_2/\text{TFMS}$)). For some substances the peak heights diminished during consecutive sweeps due to the formation of a film on the electrode. The substances with which this occurred were those with free orthopositions in the phenolic part or with one or three methoxyls in the ether part. In most cases (except 12 and 14) good preparative results could still be obtained.

No.	R ₁	R ₂	R ₃	R ₄	Ep1/2(E)	n	R ₅	Ep1/2(P)	Ep1/2(E-(CH ₂) _n -P)	No.
6	H	OMe	OMe	H	1.19	3	OMe	0.85	0.74	19
7	H	OMe	OMe	H	1.19	3	Me	1.10	0.99	20
8	Me	H	OMe	OMe	1.32	3	H	1.27	0.99	21
9	H	OMe	OMe	H	1.19	3	H	1.27	1.09	22
10	H	OCH ₂ O	H	H	1.17	3	H	1.27	1.13	23
11	H	OMe	OMe	H	1.19	3	tBu	1.23	1.13	24
12	H	OMe	OMe	OMe	1.11	3	H	1.27	1.14	25
13	H	H	H	OMe	1.54	3	tBu	1.23	1.15	26
14	H	H	H	OMe	1.54	3	H	1.27	1.21	27 + 28
15	H	H	OMe	OMe	1.19	2	H	1.27	1.11	
16	H	H	H	OMe	1.54	2	H	1.27	1.24	
17	H	H	OMe	OMe	1.19	4	H	1.27	1.13	
18	H	H	H	OMe	1.54	4	H	1.27	1.16	

Figure 4

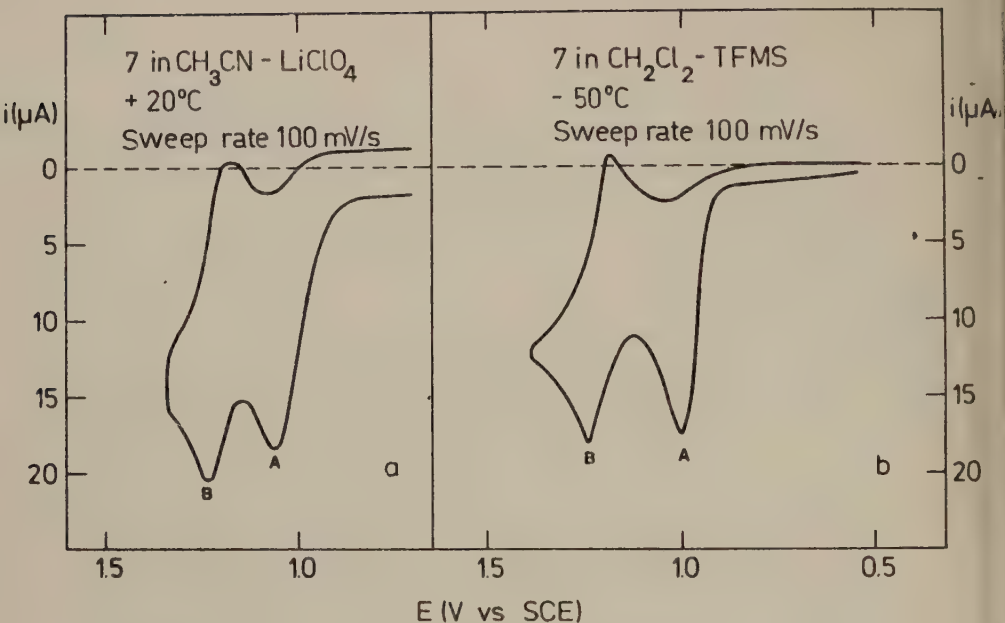
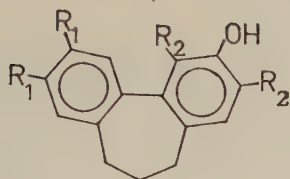


Figure 5

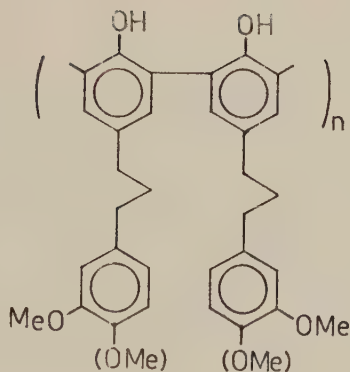
Constant current coulometry¹¹ on 6 - 11 and 13 showed in all cases that peak A (cf. Fig. 5) corresponds to a 2e oxidation. During coulometry peak B remained unchanged indicating that it corresponds to oxidation of a product formed at peak A. Addition of dienones 19 - 24 and 26 resulted in an increase in peak B indicating that the product formed at peak A is the dienone.

4:3 Preparative results.

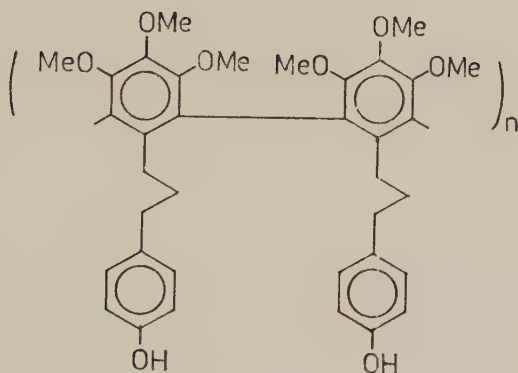
Preparative experiments were conducted in both $\text{CH}_3\text{CN}/(\text{CH}_3)_4\text{NBF}_4$ and $\text{CH}_2\text{Cl}_2/\text{TFMS}/(\text{nBu})_4\text{NBF}_4$. The new chemical reagent thallium tris-(trifluoroacetate) (TTFA) was also tested on all substances. On electrolysis in $\text{CH}_2\text{Cl}_2/\text{TFMS}$ coupled products like 29 were obtained rather than dienones. By adding dienones to $\text{CH}_2\text{Cl}_2/\text{TFMS}$ and observing the solutions with voltammetry it was shown that they rearrange (phenol-dienone rearrangement) to product 29.



29



30



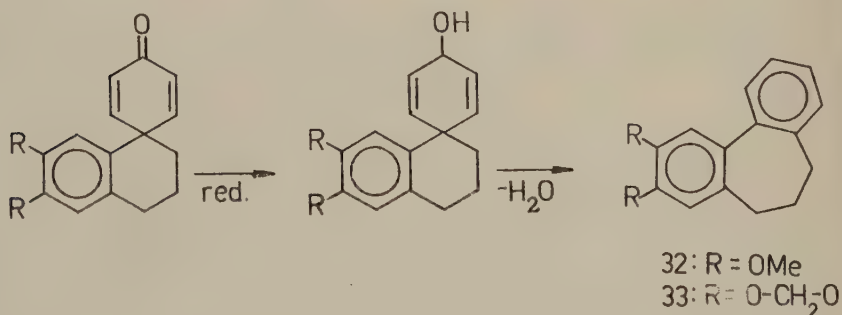
31

The substances 12 and 14 gave polymeric products only; these passivated the electrode so that it had to be cleaned several times in order to get the desired amount of current through the solution.

These polymers are probably 30 and 31. (In the case of 31

this was actually observed in PMR. Since electrolysis of 13 gives a high yield of dienones without filming the identity of 30 is quite certain even though no spectral data were obtained.) Oxidation of 8 in $\text{CH}_2\text{Cl}_2/\text{TFMS}$ gives neither (rearranged) dienones nor polymers. The identity of the product is uncertain but according to PMR the methyl substituent at position-1 appears to have been attacked

During preliminary experiments (paper I) 32 and 33 were isolated. Presumably these compounds have arisen by what could be called a dienol-benzene rearrangement of the reduced dienone¹².



Similar rearrangements have been observed in the biosynthesis of certain alkaloids e.g. in the formation of the aporphine alkaloids anonaine and roemerine^{6,13}.

In the first preparative experiments, passivation of the anode was a very annoying problem. Even with substances 8, 9 and 10 the electrolyses were unpredictable. Many experiments were therefore carried out in order to find the reason. It turned out that the stirring rate was the crucial factor. When stirring was very slow filming was no problem in the oxidation of 8, 9 and 10. The filming was interpreted as a result of formation of polymers such as 30 from phenoxy-

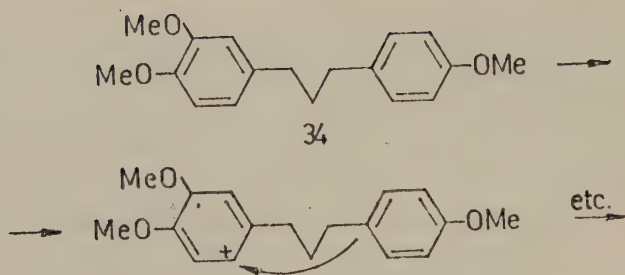
radicals. Dimerisation of radicals is known to be a very fast reaction¹⁴ and even a small amount of phenoxyl radicals in the vicinity of the anode would quickly form a monomolecular layer. If the concentration of phenoxyl radicals is very low however it should be possible to oxidise them further to phenoxonium ions simply by lowering the concentration of substrate and not letting the phenoxyl radicals escape from the double layer. Slower stirring reduces diffusion both to and from the anode and is consequently beneficial in both respects.

4:4 Discussion.

Disregarding differences in charge-transfer rates, adsorption, solvation etc. a difference between the oxidation potentials for the phenolic-(Ep(P)) and the phenol ether part (Ep(E)) in $\delta - 18$ greater than 100 mV should permit selective (>95%) oxidation of one part. (This can be concluded from the Butler-Volmer equation¹⁵.) The discussion of preparative, results below derives from this fact.

Ep(P) - Ep(E) > 100 mV

The only compound in this category is 12; here the ether part should be oxidised selectively. As was noted above, 12 yields only the polymer 31, probably via coupling of radical cations from the ether part. This is somewhat surprising since 1-(4-methoxyphenyl)-3-(3,4-dimethoxyphenyl)propane, 34, gives coupling in high yield by intramolecular attack on a radical cation. (See page 20, paper III.)



The nucleophilicity of the unoxidised part is probably of the same magnitude in **12** and **34** so the reason for the difference in behaviour must be sought elsewhere. One possible reason is that in the radical cation from **12** the positive charge is more evenly distributed over the ring due to the presence of an extra methoxy-group. This should result in less repulsion between the charged rings (aiding intramolecular coupling) and smaller electrophilicity (diminishing intramolecular coupling). It is also possible that the extra methoxy-group in **12** makes this compound sufficiently nucleophilic to be able to couple intermolecularly.

$$E_p(E) - E_p(P) > 100 \text{ mV}$$

In substances **6**, **13** and **14** the phenolic part is selectively oxidised. The coupling is very probably achieved by nucleophilic attack on a phenoxonium ion since the initially formed radical is a poor electrophile. With **14**, only traces of spirodienone were obtained and excessive filming occurred. (Compare **30**.) With the phenoxy-radical formed initially from **14** there is probably competition between further oxidation and radical coupling. In **13** the ortho positions in the phenol part are blocked and no problem with filming is encountered. Unfortunately it is difficult to assess the relative significance of the two competitive reactions. The

coupling of radicals need not however be very significant to be able to deactivate the anode.

$$|E_p(E) - E_p(P)| > 100 \text{ mV}$$

For the substances 7 - 11 there are in principle three paths in which intramolecular coupling can occur giving spirodienones.

- a) Nucleophilic attack on a phenoxonium ion, by the unoxidised ether part.
- b) Coupling between a radical cation (from the ether part) and a radical (from the phenol part)
- c) nucleophilic attack on a radical cation (from the ether part) by the unoxidised phenol part.

When oxidising phenols in a very acidic medium such as TFMS in CH_2Cl_2 it is possible to reach the reversible oxidation potentials for the phenols. This is done by hindering deprotonation of the initially formed radical cation. In such a medium the phenol thus behaves as a phenol ether. Substances 7, 9 and 10 show very similar behaviour in voltammetric and preparative experiments both in CH_3CN and in $\text{CH}_2\text{Cl}_2/\text{TFMS}$. This proves definitely that it is possible to obtain spirodienones by path c, but gives no information about whether this is really the case in CH_3CN . Substance 8 exhibits different behaviour in both solutions and thus can not be forced to react along path c. Compounds 8, 9 and 10 are very dependent on the stirring rate and the formation of spirodienones in CH_3CN in these cases probably partly proceeds by path a. The fact that it is possible to avoid filming merely by using a slow stirring rate must mean that concentration of radicals is very low in the double layer and path a is probably of only minor importance. The most probable mechanism for the cyclisation of 8 is thus path b. Since the phenol ether is oxidised at lower potential in 9, 10 and 11 relative to 8, path b must be considered as the most probable mechanism for cyclisation of the latter substances also. However, further experiments are needed to clarify this point.

5. PART B.

ANODIC CYCLISATION OF PHENOL ETHERS

5:1 Introduction to papers III and IV.

As has been pointed out previously radical cations from phenols are very acidic and revert to radicals in all but the most acidic media. These have the disadvantage that they induce rearrangements of the products first formed. In order to study whether radical cations can serve as electrophiles in cyclisations it is therefore better to use phenol ethers whose radical cations are relatively stable in non-nucleophilic media.

5:2 Paper III.

Paper III deals with the anodic oxidation of **34**. When oxidising **34** in $\text{CH}_3\text{CN}/\text{LiClO}_4$ the product pattern changes drastically with the potential. At high potential (~ 1.6 V vs SCE) the dienone **35** was isolated in 70% yield. At low potential (~ 1.25 V vs SCE) the coupled phenol ether **36** was isolated in almost quantitative yield.



34

The cyclic voltammogram of **34** in $\text{CH}_2\text{Cl}_2/\text{TFA}$ 3:1 is shown in Fig. 6.

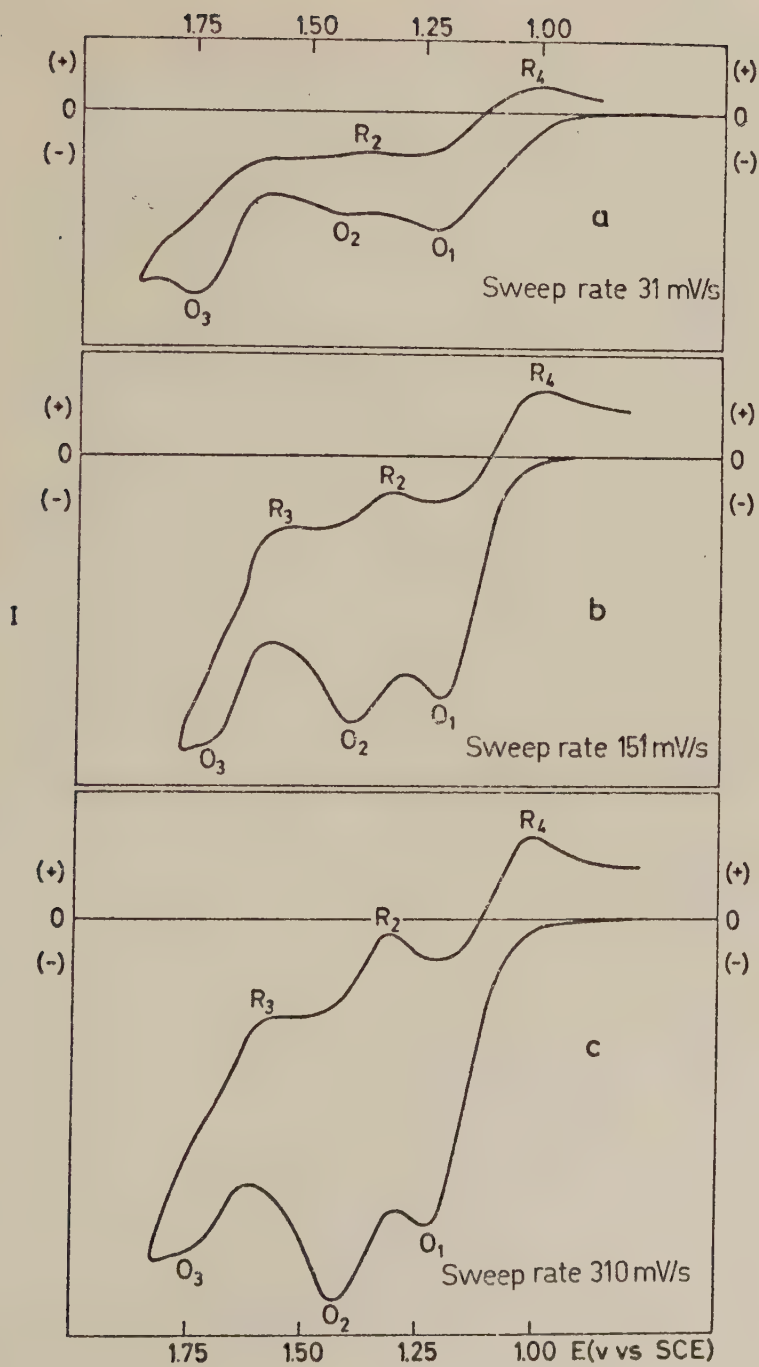


Figure 6

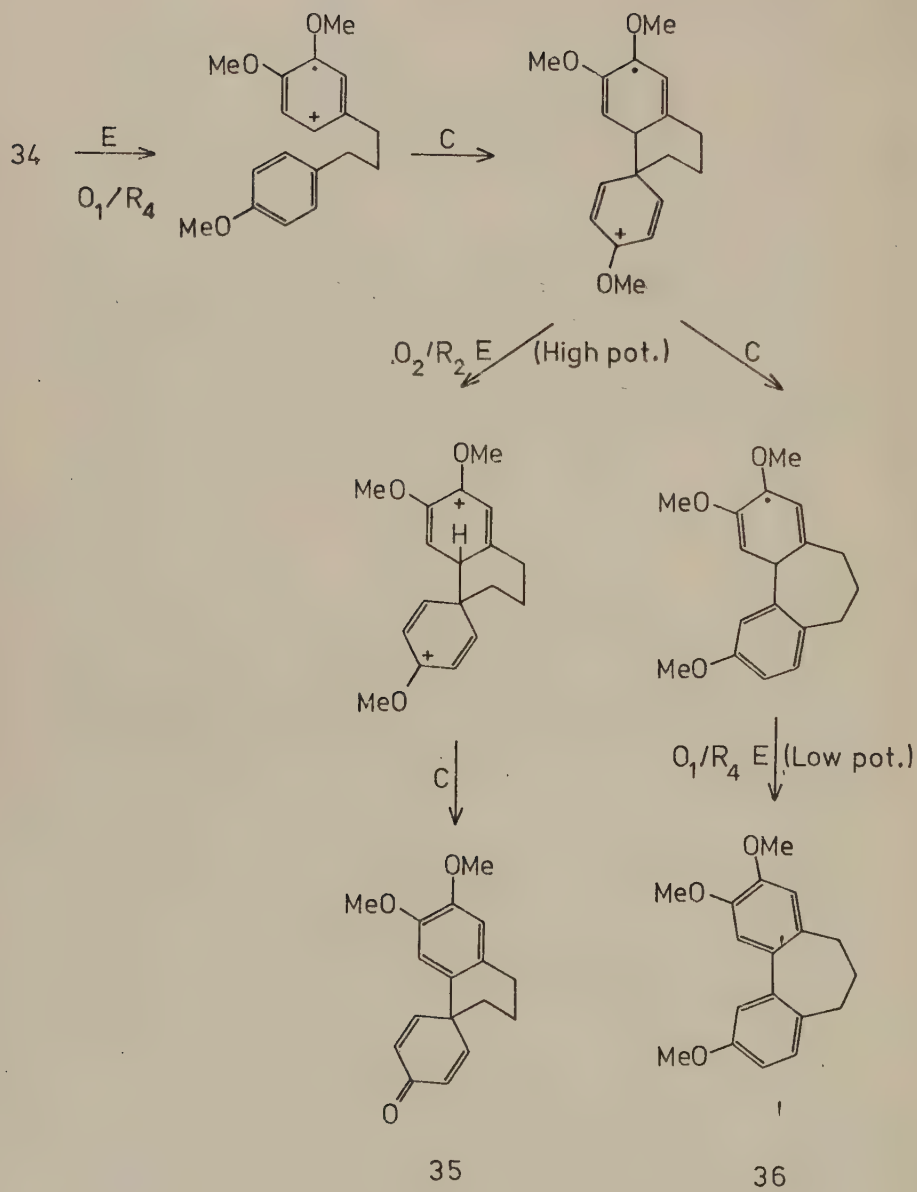
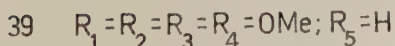
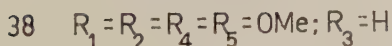
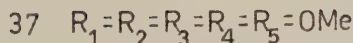
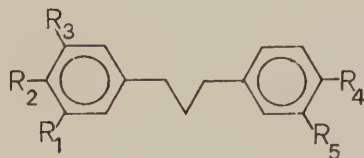


Figure 7

The voltammogram consists of three oxidation peaks at about 1.20 (O_1), 1.40 (O_2), 1.70 (O_3) V vs SCE and three reduction peaks at 1.60 (R_3), 1.30 (R_2) and 1.10 (R_4). The relative peak heights are very dependent on sweep rate. (The peak currents automatically increase with sweep rate since the amount of oxidised material is the same but the rate is faster. The relative change is therefore the most significant parameter in this discussion.) Thus O_2 (Fig. 6) increases and O_3 decreases in relation to O_1 with increasing sweep rate. At 600 mV/sec the peak current at O_2 appears to be the same as O_1 and the two peaks most probably correspond to two consecutive 1e transfers. O_2/R_2 is a reversible redox couple of a short-lived intermediate formed during oxidation of 34 to 35. (Lifetime about 1 sec. in CH_2Cl_2 /TFA 3:1.) The voltammogram of 34 in acetonitrile shows similar results; O_2 shows a marked sweep rate dependence. The peak R_2 however is never seen, irrespective of sweep rate, indicating that the intermediate formed at O_2 is rapidly consumed in a chemical reaction.

The observation from voltammetry and from preparative experiments are interpreted as shown in Fig. 7.

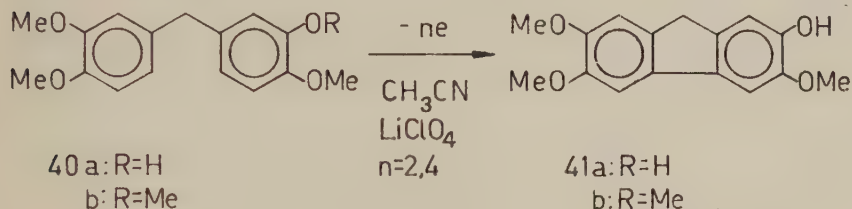
In an effort to study this reaction in greater detail various methoxylated 1,3-diphenylpropanes were prepared.



Voltammetry as well as preparative results for the substances 37 - 39 showed no resemblance to the results from oxidation of 34. Substances 37 and 38 gave cyclised product such as 36 almost quantitatively regardless of the potential. Substance 39 gives neither cyclised products such as 36 nor spirodienones but; instead it forms intermolecularly coupled products. (Compare the corresponding oxidation of phenols, page 15, substance 31.) The outcome of the oxidation therefore seems to be critically dependent on the relative oxidation potentials of the two rings, the nucleophilicity of the unoxidised ring and the electrophilicity of the oxidised ring.

5:3 Paper IV.

Radical cations and phenoxoniumions have been observed directly in a few cases^{7,16}. Paper IV concerns the oxidation of the substance 41a from which the radical cation, the phenoxoniumion and under special circumstances even the dication can be observed.



The cyclic voltammogram of 41a in $\text{CH}_2\text{Cl}_2/\text{TFA}$ 3:1 and in $\text{CH}_2\text{Cl}_2/\text{TFA}/\text{TFMS}$ (45:3:2) is shown in Fig. 8.

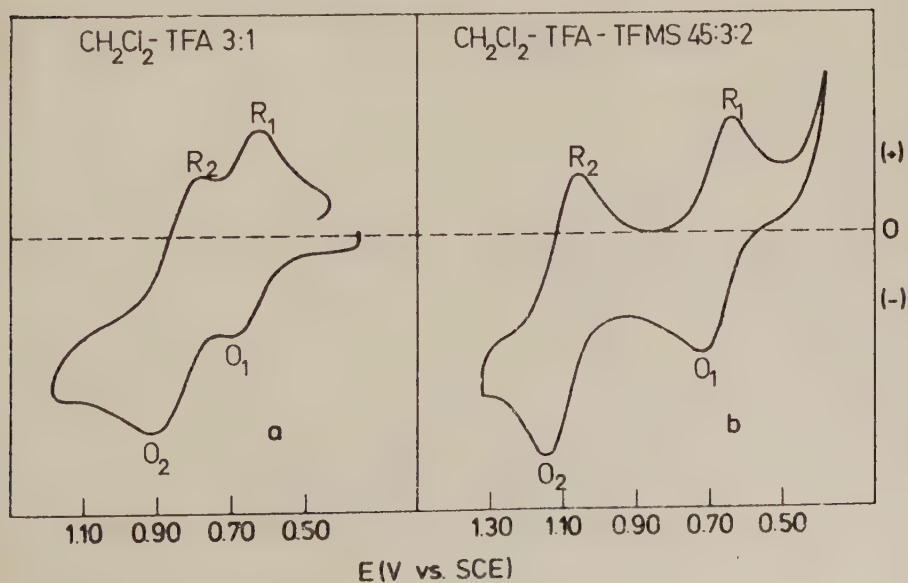


Figure 8

Fig. 8a shows a reversible oxidation-reduction couple (O_1/R_1) at low potential and a quasi-reversible pair of peaks (O_2/R_2) at higher potential. In Fig. 8b both O_1/R_1 and O_2/R_2 appear as reversible couples. In this case O_2/R_2 is quasi-reversible, however, since the peak separation between O_2 and R_2 decreases with increasing sweep rate. O_2-R_2 must therefore be coupled to a chemical step, i.e. deprotonation-protonation.

The voltammograms are interpreted as shown in Fig. 9.

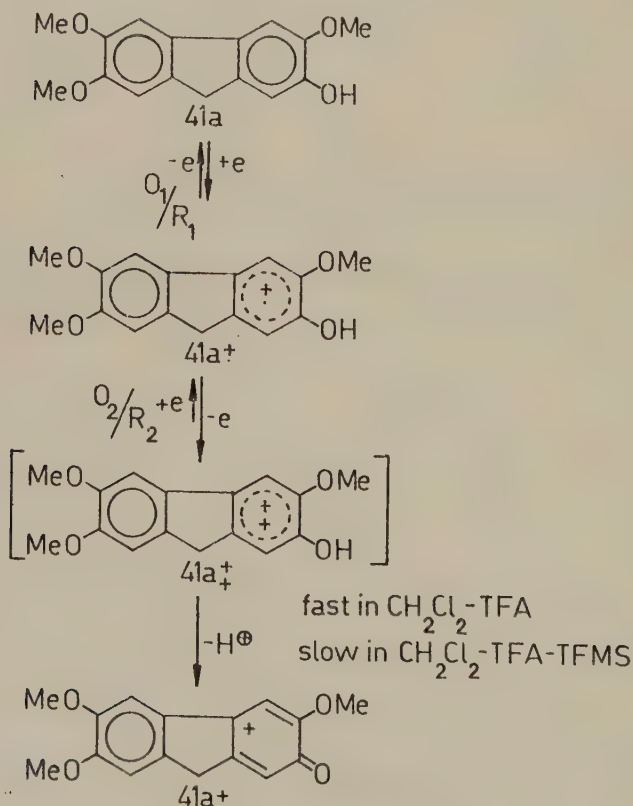
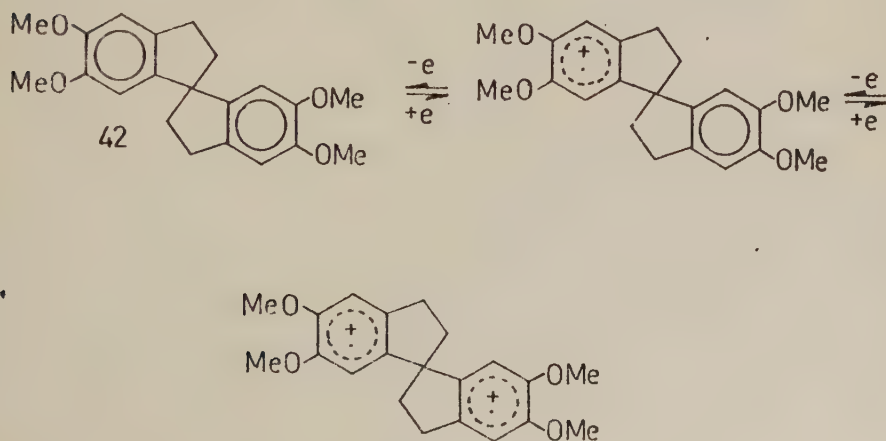


Figure 9

A 1e oxidation of *41a* in $\text{CH}_2\text{Cl}_2/\text{TFA}$ 3:1 gave $41a^+$ in high yield. Addition of TFMS to a solution of *41a* in CH_2Cl_2 gave $41a^+$ (by air oxidation). The ESR-spectra of $41a^+$ prepared chemically and electrochemically were identical. Solutions of $41a^+$ could be quantitatively converted back to *41a* by cathodic reduction. $41a^+$ is indefinitely stable in both solutions and it was isolated as blue crystals with limited stability from $\text{CH}_2\text{Cl}_2/\text{TFA}$. The reason for the remarkable stability of these species is probably the very good overlap between the 2-p orbitals of the two six-membered rings. *41a* was prepared by electrochemical oxidation of *40a* or *40b* in high yield. (By 2e and 4e oxidations respectively.)

A diphenylmethane derivative with completely different behaviour is *42*. Here the 2-p orbitals of the aromatic rings are at a 90° angle to each other. The voltammogram of *42* (Fig. 10) in $\text{CH}_2\text{Cl}_2/\text{TFA}$ 4:1 shows two reversible 1e oxidation peaks separated by 0.18 V. The first corresponds to formation of a radical cation. The second peak corresponds to formation of a diradical cation. Further investigation of this system is in progress.



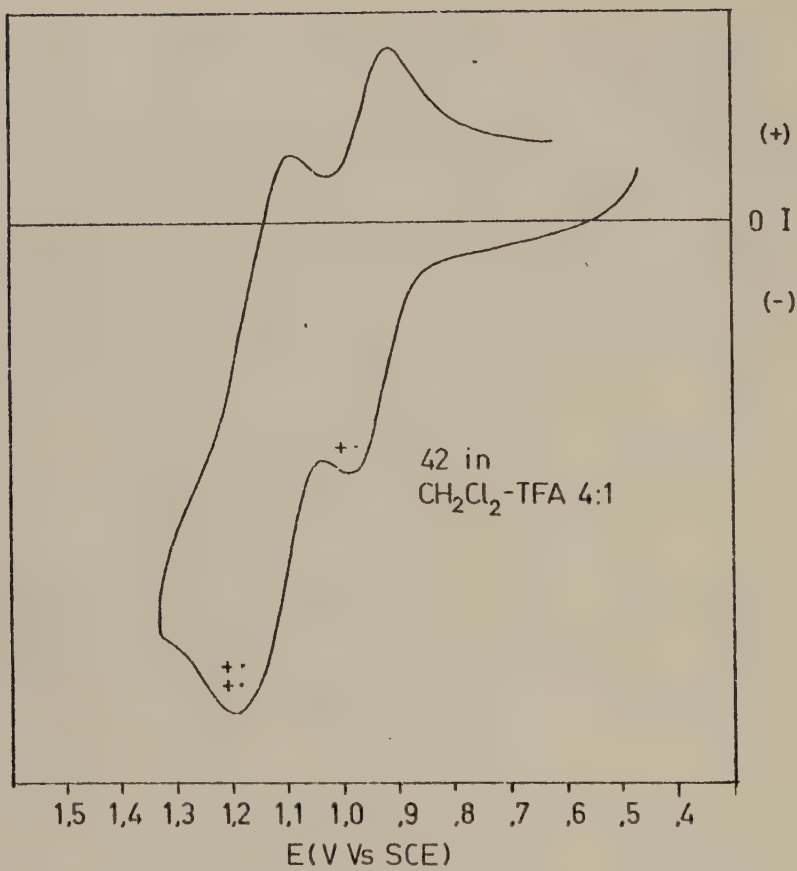
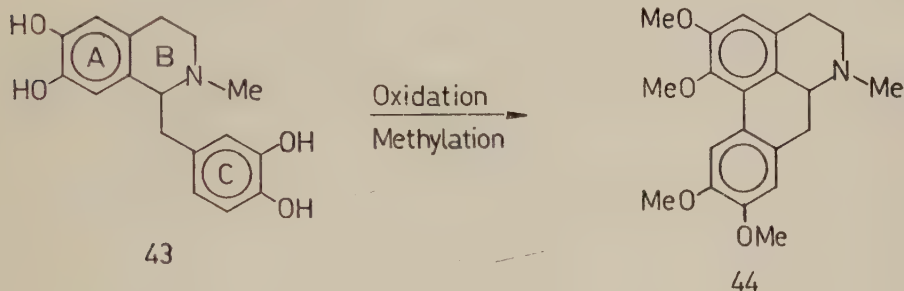


Figure 10

5:4 Introduction to paper V.

The probability that phenolic oxidations were involved in the biogenesis of alkaloids was suggested a long time ago. In 1911 Gadamer¹⁷ drew attention to the relationship between laudanosoline (43) and glaucine (44). Since then very extensive tracer experiments have provided confirmation

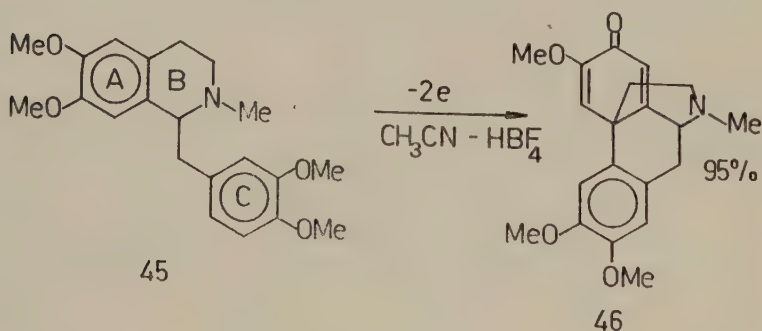


that phenolic oxidation is an important step in the biogenesis of isoquinoline¹⁸.

Many reagents have been used to effect biogenetic type syntheses of various isoquinoline alkaloids. Among these can be mentioned $K_3Fe(CN)_6$ in weakly basic solution¹⁹ or in a two phase system with chloroform and a basic aqueous solution²⁰, $FeCl_3$ ²¹, MnO_2 ²², $VOCl_3$ ²³, $Tl(OCOF_3)_3$ ²⁴ and anodic oxidation²⁵.

Oxidative coupling of methyl ethers of alkaloids with extrusion of a methyl radical (as in the formation of cyclohexadienone structures) is a reaction which possibly is not biogenetic in the original sense. However it is in this area that developments have been fastest during recent years. In addition to the biogenetic type reagents mentioned above (which have had limited success here), use has been made of VOF_3 in cold CH_2Cl_2/TFA ²⁶ and in particular of anodic oxida-

tion²⁷. Paper V is intended as a contribution to understanding of the underlying mechanisms in anodic oxidation of non-phenolic tetrahydro-isoquinolines, for instance the oxidation of laudanosine, 45, to the corresponding morphinandione 46²⁷.



Millers²⁸ conception of the mechanism in anodic cyclisation of laudanosine (Fig. 11) is that the nitrogen initially loses one electron. The cation radical formed is considered to delocalise its charge to ring A (compare formula 45) by homoconjugation. In this supposedly well-stabilised intermediate, the attack of ring C to effect coupling is facilitated. The concept of anchimeric assistance has been invoked to describe this mechanism. In Fig. 11 this reasoning is summarised. It is not clear whether the coupling is effected before or after the second electron transfer. (i.e. if the coupling is the result of nucleophilic attack of ring C on the radical cation or if it is a result of combination of two cation radicals.)

The main argument for this reaction scheme is that the voltammogram of 45 shows a broad peak at ~ 0.5 V (vs Ag/AgNO₃) in acetonitrile corresponding to oxidation of the amine function. Preparative oxidation at this potential gives 46 in 50-60% yield.

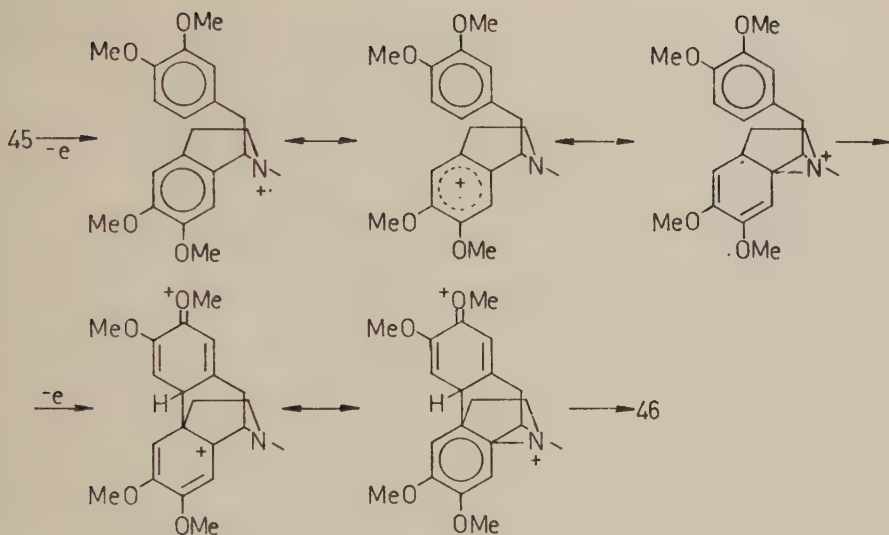


Figure 11

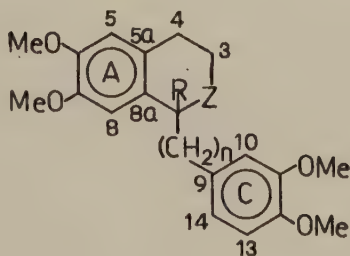
For many reasons the mechanism outline above is not fully satisfactory. For one thing the highest yields ($\sim 95\%$) are obtained in acidic (HBF_4) solution. In preparative electrolyses the area in the nearest vicinity of the electrode (i.e. in the double layer) is for natural reasons always very acidic during the oxidation of neutral compounds. Since an amine function is quite basic the potential must be controlled very careful in order to oxidise the amine function selectively.

In order to establish the function of the nitrogen it is necessary to differentiate between steric effects of ring B (formula 45) and the electronic effects of the nitrogen. The first effect can be seen on replacing the nitrogen with carbon and the second effect would, hopefully, be seen on repla-

cing nitrogen with oxygen. The ether function is oxidised at higher potential than the amine function. (In fact even higher than that of the dimethoxybenzene functions.) Therefore if similar products were obtained when oxidising the oxygen analogue of laudanosiine and laudanosiine itself it should be possible to determine the true function of the nitrogen.

In the beginning it was believed that when oxidising laudanosiine in neutral solution, a large part of the product would be glaucine (44). This product would be very quickly oxidised further (via the phenanthrene derivative) to a number of products. The basis for this assumption was earlier results on the oxidation of methoxy-substituted 1,2-diphenyl-ethanes²⁹. Substances with a methyl group situated at position-1 were therefore made. In these substances the phenanthrene cannot be formed and it should therefore be possible to isolate products coupled in the same way as glaucine 44.

The substances chosen as model compounds are shown below (47a-e).



47

a: Z=CH₂; R=H; n=1

b: Z=CH₂; R=Me; n=1

c: Z=O; R=H; n=1

d: Z=O; R=Me; n=1

e: Z=CH₂; R=H; n=2

The preparation of 47a-e is summarised in Fig. 12.

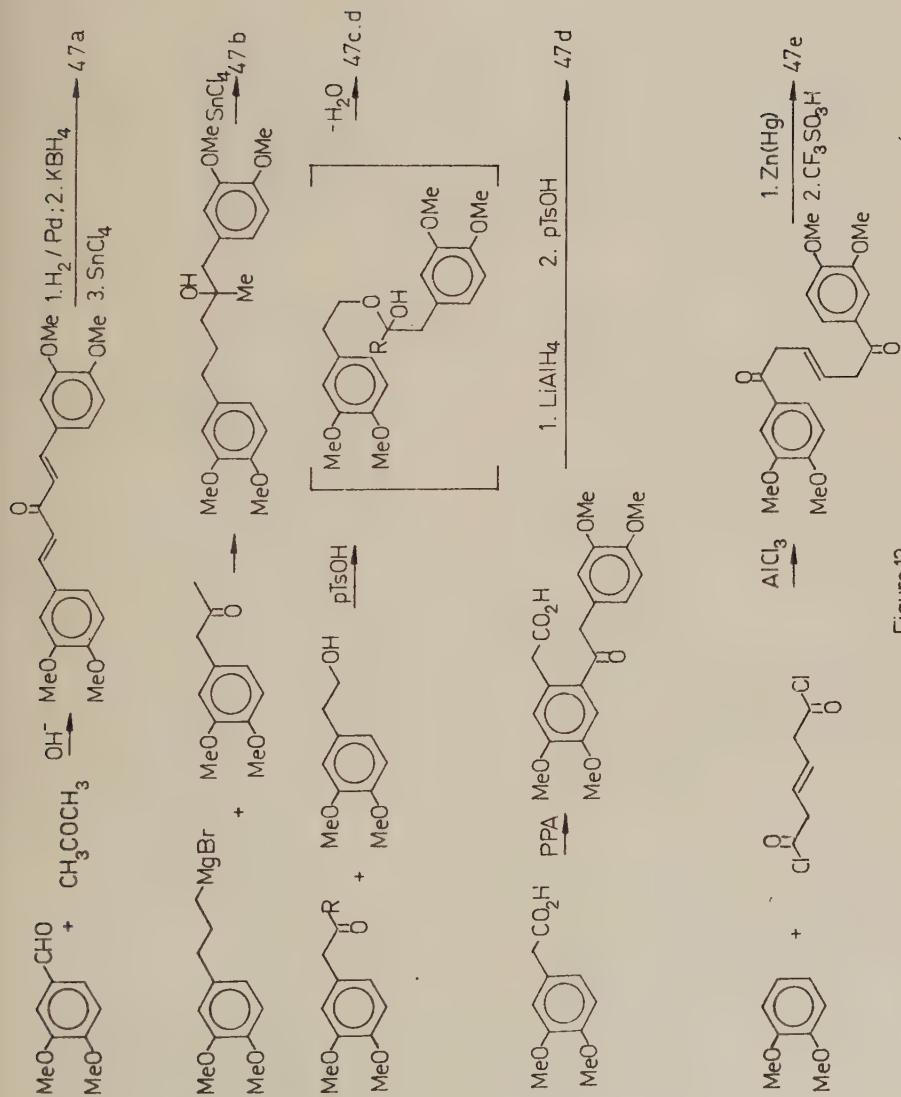
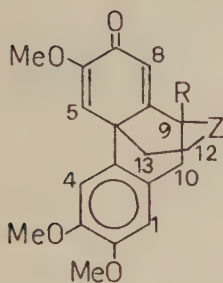


Figure 12

5:5 Preparative results.

The products obtained from preparative electrolysis of 47a-e are the substances 48-58. The electrolyses were conducted essentially in three systems $\text{LiBF}_4/\text{CH}_3\text{CN}$, HBF_4 (35% in H_2O)/ CH_3CN and $(\text{nBu})_4\text{NBF}_4/\text{CH}_2\text{Cl}_2/\text{TFA}$. With these systems it is possible to obtain a great deal of selectivity in the oxidation of 47a-e. The preparative results may be summarized as follows.

Substrate	Medium	Products
47a,b	$\text{LiBF}_4/\text{CH}_3\text{CN}$	All three types of dienones. 48a,b and 49a,b dominating.
"	$\text{HBF}_4/\text{CH}_3\text{CN}$	Dienones 48a,b and 50a,b. 48a,b dominating
"	$(\text{nBu})_4\text{NBF}_4/\text{CH}_2\text{Cl}_2/\text{TFA}$	o,p-coupled products 52 and 53b.
47c,d	$\text{LiBF}_4/\text{CH}_3\text{CN}$	Hydroxylated substances 54a,b. No dienone.
"	$\text{HBF}_4/\text{CH}_3\text{CN}$	Hydroxylated substances 54a,b and dienone 48c,d
"	$(\text{nBu})_4\text{NBF}_4/\text{CH}_2\text{Cl}_2/\text{TFA}$	No products isolated.
47e	$\text{LiBF}_4/\text{CH}_3\text{CN}$	Dienone 49c sole product
"	$\text{HBF}_4/\text{CH}_3\text{CN}$	" " " "
"	$(\text{nBu})_4\text{NBF}_4/\text{CH}_2\text{Cl}_2/\text{TFA}$	o,p-coupled substance 53c sole product.



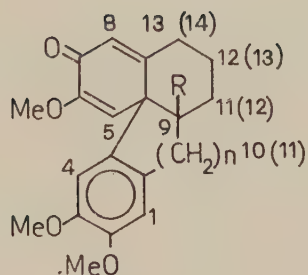
48

a: $Z=CH_2$; $R=H$

b: $Z=CH_2$; $R=Me$

c: $Z=O$; $R=H$

d: $Z=O$; $R=Me$

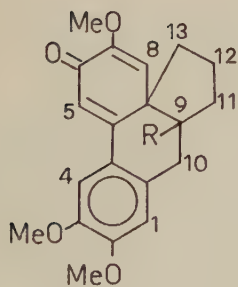


49

a: $R=H$; $n=1$

b: $R=Me$; $n=1$

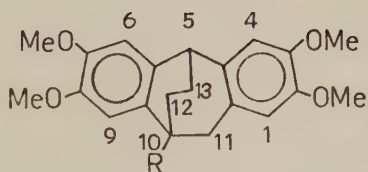
c: $R=H$; $n=2$



50

a: $R=H$

b: $R=Me$



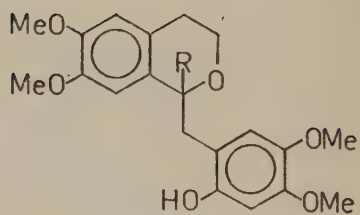
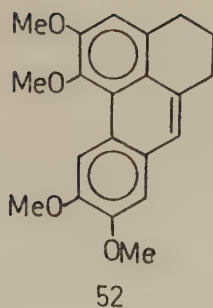
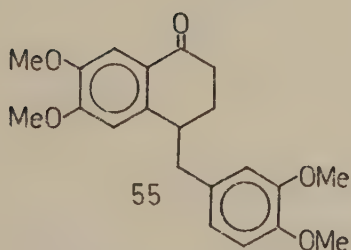
51

a: $R=H$

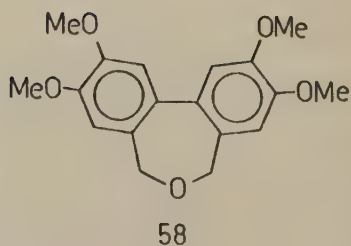
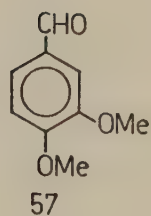
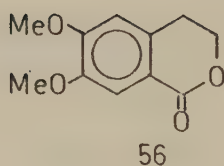
b: $R=Me$



53 a: R = H; n = 1
 b: R = Me; n = 1
 c: R = H; n = 2



54 a: R = H
 b: R = Me



5:6 Polarography.

In cyclic voltammetry 47a-e all behave in a very similar way. Fig. 13 shows a typical example. The voltammogram con-

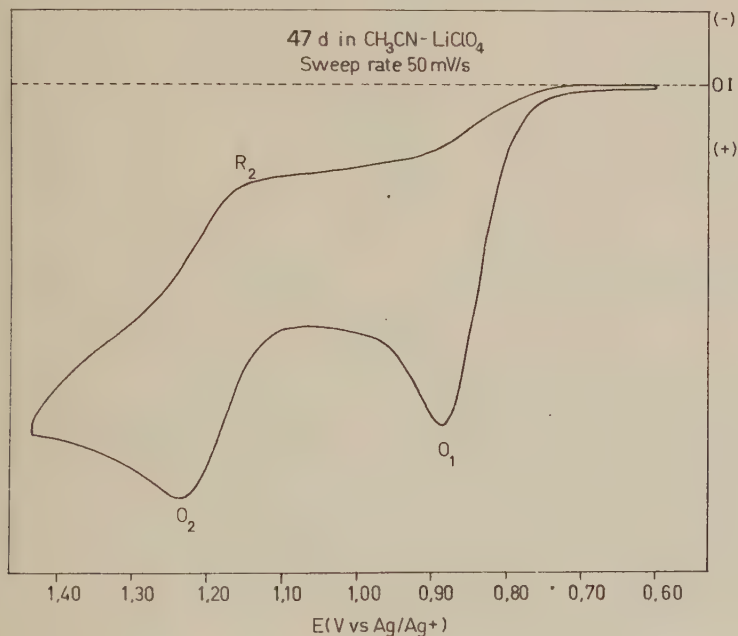


Figure 13

sists of an irreversible oxidation peak O_1 at ~ 0.8 V (vs Ag/AgNO_3) and a quasi-reversible peak O_2 at ~ 1.2 V. O_1 corresponds according to constant current peak coulometry¹¹ to a 2e oxidation. The oxidation at O_1 is probably an ECE-process since the second harmonic ac-voltammograms, showing ~ 68 mV peak to peak separation, were those expected for a reversible one electron transfer. According to second harmonic ac-polarography the second peak O_2 also corresponds to a 1e-oxidation.

The oxidation potentials for the initially formed ECE- intermediates are in all cases greater than the oxidation potentials for the products as shown for example by 47a.

Substrate/electrolysis

product.	E_{rev} (Volts) ^x
47a	0.800; 0.930; 1.050; 1.185
48a	0.955
49a	0.970
50a	Not obtained
51a	0.795; 0.920
53	0.595
55	0.855

^xObtained in $\text{CH}_3\text{CN}/(\text{nBu})_4\text{NBF}_4$; ac-polarography vs Ag/AgNO_3

It is well known³⁰ that cations derived from aromatic compounds are oxidised at more positive potentials than the compounds themselves. It therefore appears reasonable to ascribe structures 59a, 60a and 61a (Fig. 14) to these cationic intermediates. The three peaks at higher potential in the oxidation of 47a correspond to oxidation of ring C in these intermediates to give radical dications.

5:7 Discussion of mechanisms.

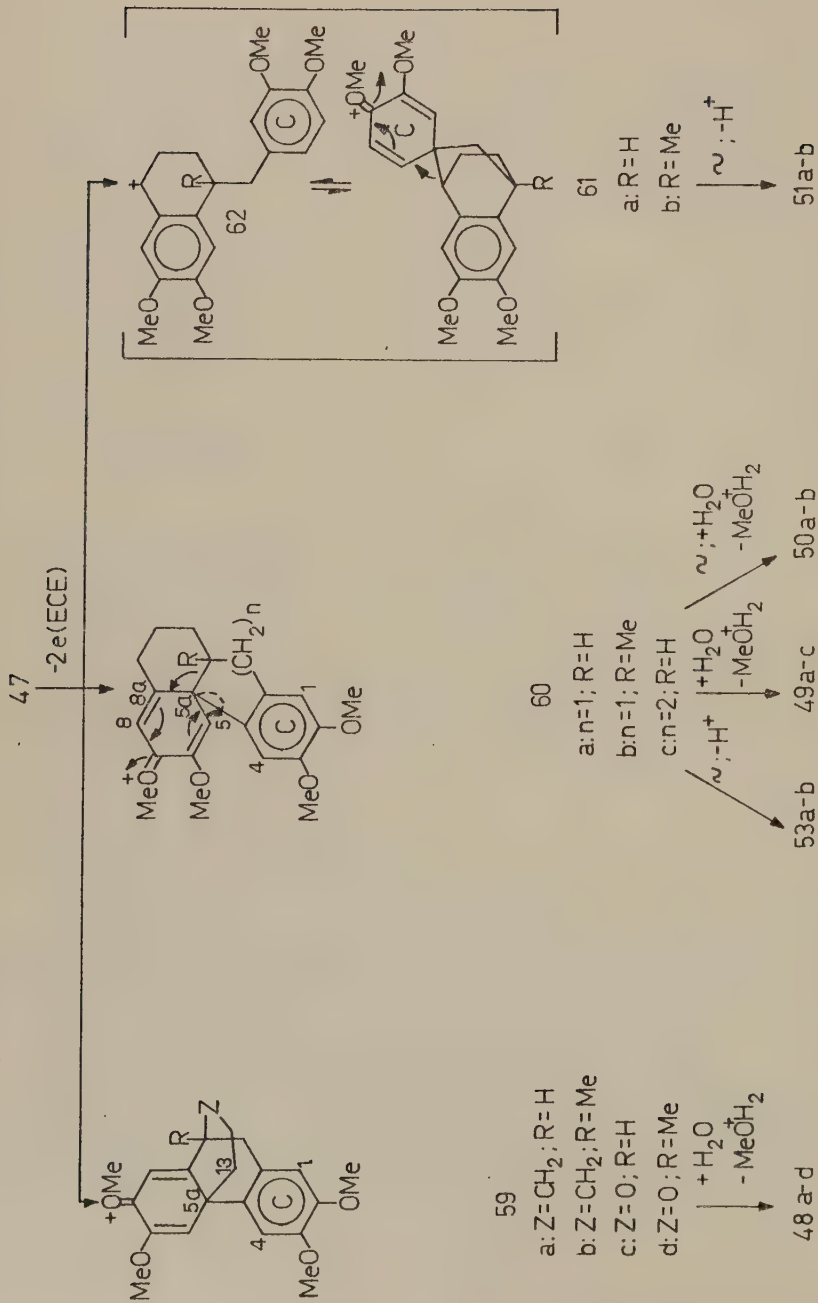
The formation of 48a can be explained, as shown in Fig. 14, as a result of nucleophilic attack (of water or acetonitrile) on 59 followed by elimination of MeOH^+ . In the same manner 49a can be formed from 60. Substances 53 and 50 are probably also formed from 60. In the case of 53 this product is formed after rearrangement and deprotonation of 60 as shown by the dotted arrow. 50 is also obtained after rearrangement of 60 as indicated by the solid arrow. This latter type of rearrangement has also been found in other cases³¹.

In the oxidation of *47a* and *47b* in $\text{HBF}_4/\text{CH}_3\text{CN}$ dienones *49a* or *49b* were not isolated. The reason for this is most probably that *49a* and *49b* readily rearrange to o,p-coupled products of type *53a* and *53b*. These compounds when formed should be further oxidised very easily.

The product with benzylic coupling, *51*, is probably formed from an intermediate such as *61* or *62*. On oxidation of *47a* in $\text{NaOMe}/\text{CH}_3\text{CN}$ the tetralone *55* is obtained. This is a clear indication of the possible existence of an intermediate such as *62*³². The formation of dienones *48c,d* from the oxygen analogues of laudanosine can also be rationalised as in Fig. 14. However these dienones are only formed in $\text{HBF}_4/\text{CH}_3\text{CN}$. Oxidation of *47c,d* in $\text{LiBF}_4/\text{CH}_3\text{CN}$ gives only hydroxylated, *54a,b* and cleaved, *56* and *57*, compounds.

An attempt to explain this is shown in Fig. 15. Substances *54a,b* can be formed in two ways. In one of these, ring C is first oxidised to a radical cation. This radical cation *47⁺* is attacked by the oxygen in ring B and further oxidised to the oxoniumion *63*. Nucleophilic attack by water (during work up) gives *54a,b*. In the other mechanism the cation *59* is formed after a 2e-oxidation of *47c,d*. When water and protons are present the dienones *48c,d* are formed (as in Fig. 14). (Formation of *48c,d* from *59* is probably facilitated by the HBF_4 -water electrolyte, due to the acidity, which lowers the nucleophilicity of the ring B oxygen and to the water, which helps in cleaving *59* to *48c,d*. The high yield obtained on electrolysing laudanosine, *43*, can probably be explained in the same way.) When water and protons are absent *59* rearranges to *63* which then gives *54a,b* as mentioned above.

The cleavage products *56* and *57* are probably formed after oxidation of the hydroxylated substance *65* which is formed by attack of water on the benzylic cation *64*.



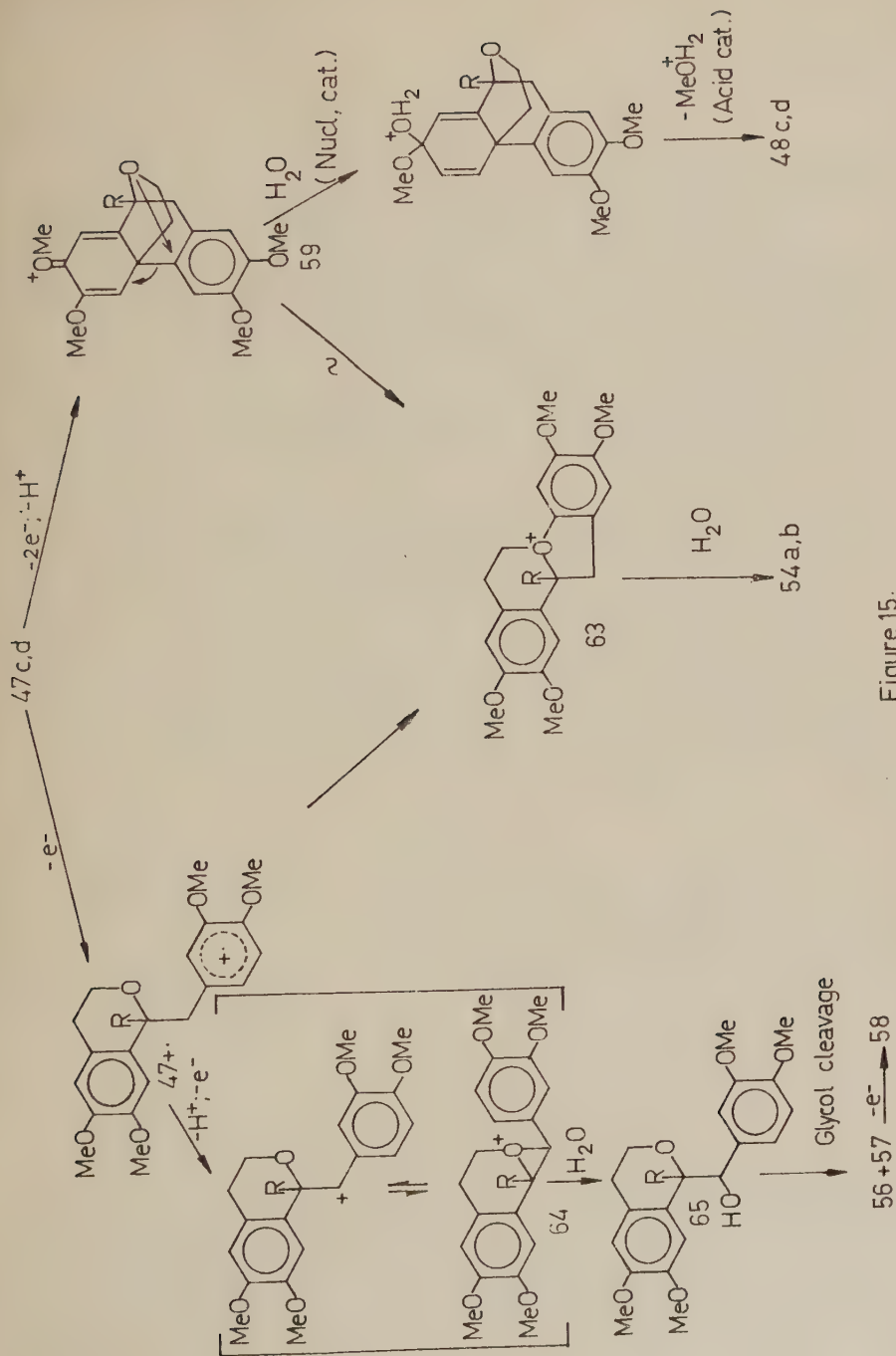
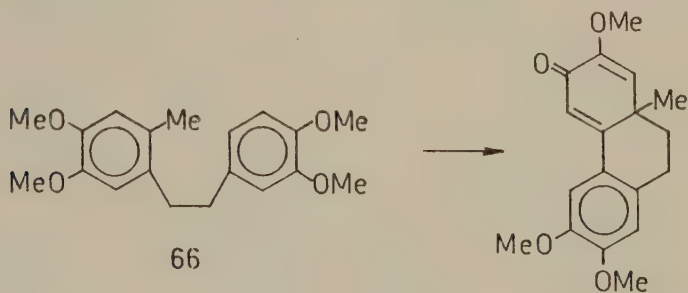


Figure 15.

5:8 Conclusions.

It is interesting to note that the coupling in *47a-e* always occurs at the C-14 position in ring C and that no C-10 coupling is observed. In ring A however, coupling to all three of the positions C-5a, C-8a and C-8 is observed. These experiments do not seem to support any possibility of a biogenetic type synthesis of morphine. (The C-10 - C-5a coupled products are those expected in the biosynthesis of morphine.) However from paper I (structure 21) it is known that o,p-coupling can be achieved when the para-positions in the phenol ether part are blocked. It would therefore be very interesting to see if it is possible to obtain C-10 - C-5a coupling with *47a-e* (and of course 45) properly substituted at C-14.

Ring B in structure 47 does not appear to put any steric restraints on the coupling between rings A and C, since the same types of products and the same yields are obtained in the anodic coupling of compounds of structure 66³¹.



The electronic effect of the heteroatom in ring C is more difficult to ascertain. Since *47a* gives *48a* in higher yield than *47c* gives *48c* it might be concluded that the oxygen in ring C of *47c* is unimportant or even a negative factor in the formation of *48c*.

However 48c is only formed in acidic-nucleophilic ($\text{HBF}_4/\text{H}_2\text{O}$) media or nucleophilic (H_2O) media. One reason for this is probably as mentioned, that protonation (or deactivation) of the ring B heteroatom hinders (or delays) rearrangement of 59. Another reason is probably that water (or some nucleophile) can cleave 59 by nucleophilic attack. These effects should be much greater in laudanosine, 45, this is probably the main reason why the electrolysis is so successful here. In any case the results obtained in paper V do not give any support to a mechanism such as that proposed by Miller²⁸.

The methyl substituent at the position-1 in 47b and 47d seem to be relatively unimportant. 47b and 47d give higher yields of dienones than 47a and 47c but this is most probably a steric effect. In 47b and 47d the methyl substituent at C-1 should force ring C to lie nearer 8a and 5a (under ring B; compare formula 47) thereby facilitating coupling at these positions.

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